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Office of Vermont Health Access

Therapeutic Class Review
N-methyl-D-aspartate (NMDA) Receptor Antagonist

Overview/Summary

Alzheimer's disease (AD) is a progressive disease that affects both cognition and behavior. AD is classified under Delirium, Dementia, and Amnestic and Other Disorders in the American Psychiatric Association's *Diagnostic and Statistical Manual for Mental Disorders*, Text Revision, 4th edition (DSM-IV-TR).[1] It is defined as the development of multiple cognitive deficits manifested by memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1] Pathophysiologic mechanisms behind the disease are not entirely understood, but a common pathologic finding is the accumulation of beta-amyloid proteins in the brain. Subsequently, inflammatory and free radical processes eventually result in neuron dysfunction and death. Although research is looking at preventing plaque formation or enhancing plaque removal, current drug therapies target symptom reduction and slow progression of cognitive and behavioral decline.

The course of the disease starts with mild cognitive impairment, progresses to more severe effects and, eventually, death, commonly due to pneumonia or aspiration. Predictors of mortality include severity at time of diagnosis, abnormal neurologic findings, and the presence of heart disease and diabetes.[2] AD is the most common of the dementias in the United States (US), accounting for more than 50% of all diagnosed dementias. It is estimated that in 2007 there were 5.1 million Americans with AD.[3]

By 2050, one in five people will be over age 65 years, and the number of Alzheimer's patients is projected to be 11-16 million.[4] Although there is no definitive diagnostic laboratory, clinical or imaging tests available, neuropsychological testing and clinical evaluation is 90% accurate. Treatment consists of nonpharmacologic and pharmacologic therapies, with nonpharmacologic interventions as the primary mechanism for management of memory loss and behavioral symptoms of AD. Nonpharmacologic therapies consist of keeping a notepad in one's pocket to make reminders, posting lists and notes throughout the house, exercising one's brain through reading and crossword puzzles, and other strategies. Current pharmacotherapy is aimed at reducing the rate of cognitive decline. Options for pharmacotherapy include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. Behavioral conditions show some improvement with these agents but, once again, treatment is geared towards reducing symptoms instead of curing or arresting the disease.

The NMDA receptor antagonist memantine effects the transmission of glutamate by weakly and noncompetitively blocking cation channels on the glutamate neuron. This weak binding does not allow for chronic stimulation which may damage neurons but does allow for bursts of excitation allowing for appropriate signal transmission.[5] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of brain cells in AD patients. This agent appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional and global deterioration apparent in patients with moderate-to-severe AD.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Memantine (Namenda®)	N-methyl-D-aspartate (NMDA) Receptor Antagonist	-

Indications

Table 2. Food and Drug Administration Approved Indications[6]

Indication	Memantine
Moderate-to-severe dementia of the Alzheimer's type	✔

Potential off-label uses may include the treatment of attention deficit hyperactivity disorder or vascular dementia.[7]

Pharmacokinetics

Table 3. Pharmacokinetics[6]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Memantine	Highly absorbed	Hepatic, partially	Renal (48) unchanged in urine	3 with minimal activity	60-80

Clinical Trials

Until recently, there were no head-to-head trials comparing the efficacy of the different agents used to treat Alzheimer's disease (AD). Limited comparative data is now available; however, data comparing memantine to other agents is not available. Memantine has been studied in combination with donepezil and galantamine. In addition, memantine has been studied in Europe during the last decade for the treatment of dementia, and was approved in the European Union in May of 2002 for the treatment of moderately severe and severe AD. In 2003, the Food and Drug Administration (FDA) gave memantine approval for the treatment of moderate-to-severe AD but not for mild AD.

Wimo et al[8] found that in moderate-to-severe Alzheimer's disease outpatients the use of memantine was associated with a significantly less amount of total caregiver time compared to placebo (51.5 hours less for the memantine group per month; 95% CI, –95.27 to –7.17; *P*=0.02). There were also fewer patients institutionalized at week 28 in the memantine group (1) compared to the placebo group (5) which was statistically significant (*P*=0.04).

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Reisberg et al[9] Memantine 10 mg twice a day vs placebo	DB, PG Patients with moderate-to-severe Alzheimer's disease	N=252 28 weeks	Primary: CIBIC-Plus and ADCS-ADL Secondary: SIB	Primary: A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL (*P*=0.03). There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score: 4.7 placebo vs 4.4 memantine; *P*=0.03), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score: 4.8 placebo vs 4.5 memantine; *P*=0.06). Secondary: Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (*P*=0.002).
Winblad et al[10] Memantine 10 mg every day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C (*P*<0.016 and *P*<0.001, respectively). Separate analyses of the Alzheimer's disease population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (*P*=0.012). Secondary: No significant differences in safety were found between the groups.
Winblad et al[11] Memantine 20 mg/day vs	MA Four studies: memantine as mono-therapy, 2 studies of	N=1,826 in subgroup with moderate-to-severe	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI	Primary: There was a statistically significant advantage for the memantine group over the placebo group in all 4 efficacy domains: CIBIC-Plus or global status (*P*<0.001), SIB or ADAS-Cog status (*P*<0.001), ADCS-ADL (*P*<0.001) and NPI (*P*=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	memantine vs placebo in patients already taking an acetylcholinesterase inhibitor Patients diagnosed with moderate-to-severe Alzheimer's disease	Alzheimer's disease 24-28 weeks	Secondary: Not reported	Secondary: Not reported
Wilkinson and Andersen[12] Memantine 20 mg/day (10 mg twice a day or 20 mg daily) vs placebo	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24-28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; *P*<0.001). Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome measure (*P*<0.001). Secondary: Not reported
Ott et al[13] Continuation of memantine up to 20 mg/day vs placebo for 8 weeks then memantine 5-20 mg/day thereafter	DB, MC, OL, PG, R Patients at least 50 years old having probable Alzheimer's disease, completed a lead-in trial that was multicenter, randomized, double-blind, placebo-controlled for 24 weeks with memantine in mild Alzheimer's disease	N=314 28 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: At least one adverse event was reported by 74.8% of patients during the 28 weeks with the most common adverse event being falls and other injuries (both 10.8%). 6.7% of patients withdrew from the study due to adverse events and the frequency was similar between the placebo-memantine group and the memantine-memantine group. Physical and lab exams were normal except for a significant increase in blood urea nitrogen levels with an incidence of 7% in the memantine-memantine group and 3.6% in the placebo-memantine group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bakchine and Loft[14] Memantine 20 mg/day vs placebo	DB, PC Patients with mild-to-moderate Alzheimer's disease	N=470 24 weeks	Primary: ADAS-COG and CIBIC-plus Secondary: Not reported	Primary: Patients in the memantine group showed a statistically significant improvement relative to placebo in ADAS-COG and CIBIC-plus at weeks 12 and 18. There was no significant difference between the groups at week 24. Secondary: Not reported
McShane et al[15] Memantine 10-30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=not specified Duration varied	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: Significant improvement at 6 months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (P=0.03); however, there was no significant difference seen for behavior and ADL scales. Significant improvement at 6 months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (P<0.00001), SIB (P<0.00001), ADCS-ADL (P=0.003) and NPI (P=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog; P=0.0002, NPI; P=0.03). Secondary: Not reported
Tariot et al[16] Donepezil (dose varied) and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	DB, MC, PC, R Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (P=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared with the progressive decline seen with the donepezil-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo treatment. The change in total mean scores favored memantine vs placebo for the CIBIC-Plus (possible score range was 1-7), 4.41 vs 4.66, respectively (*P*=0.03). Treatment discontinuations due to adverse events for memantine vs placebo were 7.4% of the patients compared to 12.4%. Secondary: Not reported
Cumming et al[17] Donepezil (dose varied) and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	DB, PC, PG, PRO Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: NPI Secondary: Not reported	Primary: NPI scores significantly favored the memantine group at 12 weeks and at 24 weeks. At week 12, NPI scores increased (worsening behavior) 1.7 points in the placebo group and decreased 2.5 points in the memantine group (*P*<0.001). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline (*P*=0.002). Fewer patients developed delusions in the memantine treatment group than the placebo group (*P*=0.011). Secondary: Not reported
Dantoine et al[18] Rivastigmine 3-12 mg/day Addition of memantine 5-20 mg/day for non-responders of rivastigmine at end of week 16	MC, OL Patients at least 50 years old with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6	N=202 16 weeks of rivastigmine monotherapy (Phase 1) Additional 12 weeks of rivastigmine and memantine	Primary: MMSE Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1. For those patients previously on donepezil or galantamine, responder rates were also similar (46.6% and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	months prior with donepezil 5-10 mg/day or galantamine 16-24 mg/day and considered not stabilized, current stabilized medications allowed	combination therapy for non-responders of rivastigmine monotherapy (Phase 2) Total 28 weeks		more significantly than those who switched from donepezil (84.2% vs 72.3%; *P*=0.047). Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (*P*<0.001 and *P*<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (*P*<0.05, *P*<0.001, and *P*<0.001, respectively).
Porsteinsson et al[19] Donepezil, rivastigmine or galantamine (doses varied) and memantine 20 mg once daily vs donepezil, rivastigmine or galantamine (doses varied) and placebo	PC, R Patients with probable Alzheimer's disease, MMSE scores between 10-22, concurrently taking a cholinesterase inhibitor	N=433 24 weeks	Primary: ADAS-cog, CIBIC-Plus Secondary: ADCS-ADL, NPI, MMSE	Primary: No significant difference in ADAS-cog and CIBIC-Plus was found between memantine and placebo. Secondary: No significant difference in ADCS-ADL, NPI or MMSE was found between memantine and placebo.
Maidment et al[20] Memantine 20 mg daily vs	MA Patients with probable Alzheimer's disease	N=1,750 Duration varied	Primary: NPI Secondary: Not reported	Primary: Compared to the placebo group patients receiving memantine improved by 1.99 on the NPI scale (95% CI, -0.08 to -3.91; *P*=0.041. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or memantine 20 mg daily in combination with a cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)				Not reported

Study abbreviations: DB=double blind, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized
Miscellaneous abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale, ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, BGP=Behavioral Rating Scale for Geriatric Patients, CGI-C=Clinical Global Impression of Change, CIBIC-Plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input, D-KEFS=Delis-Kaplan Executive Function System, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, GDS=Global Deterioration Scale, MMSE=Mini-Mental Status Exam, NPI=Neuropsychiatric Inventory, SIB=Severe Impairment Battery

Special Populations

Table 5. Special Populations[6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Memantine	Pharmacokinetics in younger and elderly patients are similar. Safety and efficacy not established in the pediatric population.	Renal dose adjustment required in patients with severe renal dysfunction.	Administer with caution in patients with severe hepatic dysfunction.	B	Unknown

Adverse Drug Events

The following table presents the most common (≥2%) adverse events reported with N-methyl-D-aspartate (NMDA) receptor antagonist. Other reported adverse drug events include agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia and arthralgia.[6]

Table 6. Adverse Drug Events[6] **(%)**

Adverse Event	Memantine
Cardiovascular	
Hypertension	4
Central Nervous System	
Confusion	6
Dizziness	7
Fatigue	2
Hallucination	3
Headache	6
Somnolence	3
Gastrointestinal	
Constipation	5
Vomiting	3
Respiratory	
Cough increased	4
Dyspnea	2
Other	
Pain	3

Contraindications / Precautions

Use is contraindicated in patients with hypersensitivity to the N-methyl-D-aspartate (NMDA) receptor antagonist or to any excipients used in the formulation.[6]

Caution should be taken in patients with neurological or genitourinary conditions as memantine has not been evaluated in patients with seizure disorders and an increase in urine pH may decrease the urinary elimination resulting in increased memantine levels.[6]

Drug Interactions

There are no significant drug interactions listed for the N-methyl-D-aspartate (NMDA) receptor antagonists.[6-7]

Dosage and Administration

Table 7. Dosing and Administration[6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Memantine	Solution and tablet:* Week 1: 5 mg once daily Week 2: 10 mg/day (5 mg twice daily) Week 3: 15 mg/day (10 mg every morning, 5 mg every night) Week 4: maintenance dose, 20 mg/day (10 mg twice daily)	Safety and efficacy not established in the pediatric population.	Solution: 10 mg/5 mL Tablet: 5 mg 10 mg 4 week titration pack

*Minimal recommended interval between dose increases is one week.

Clinical Guidelines

Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in Alzheimer's disease (AD). It is believed that the memory loss in AD is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is Food and Drug Administration (FDA) approved only for moderate-to-severe dementia and the cholinesterase inhibitors are indicated for mild-to-moderate disease with the exception of donepezil which also is indicated for moderate-to-severe disease. Rivastigmine has the additional indication of dementia associated with Parkinson's disease.[6-7]

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Neurology (AAN): **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2003)**[21]	Pharmacologic Treatment of Alzheimer's Disease (AD) • Cholinesterase inhibitors should be considered in patients with mild-to-moderate AD, although studies suggest a small average degree of benefit. • Vitamin E (1,000 IU by mouth twice a day) should be considered in an attempt to slow progression of AD. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatory or other putative disease-modifying agents specifically to treat AD because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat AD. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. Pharmacologic Treatment for Noncognitive Symptoms of Dementia • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents may be better tolerated compared with traditional antipsychotics. • Selected antidepressants (eg, selective serotonin-reuptake inhibitors and tricyclics) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. Educational Interventions for Patients with Dementia and/or Caregivers • Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with AD to delay time to nursing home placement.

Clinical Guideline	Recommendation(s)
	• Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary antipsychotics. • As part of this practice guideline, additional interventions other than education for patients and caregivers are available for functional behaviors, problem behaviors and care environment alterations.
American Academy of Neurology (AAN): **Practice Parameter: Diagnosis of Dementia: An Evidence-Based Review (2004)**[5]	Management of Dementia • Cognitive symptoms of AD are treated with cholinesterase inhibitors and vitamin E. • Cholinesterase inhibitors have been proven effective in patients with mild-to-moderate AD and vitamin E may be considered to slow progression. • Agitation, depression and psychosis should be treated initially with environmental manipulation. If this is not effective, then antipsychotics may be used. Tricyclics, monoamine oxidase inhibitors and selective serotonin-reuptake inhibitors should be considered to treat depression. • Caregiver participation in educational programs and support groups is recommended.
British Association for Psychopharmacology: **Clinical Practice with Anti-dementia Drugs: A Consensus Statement (2006)**[22]	• Cholinesterase inhibitors are effective in the treatment of mild-to-moderate AD. • One cholinesterase inhibitor should be switched to another if the first is not tolerated or effective. • Memantine is effective in the treatment of moderate-to-severe AD. • Memantine may be added to a cholinesterase inhibitor. • Cholinesterase inhibitors may be used for the treatment of both dementia with Lewy bodies and Parkinson's disease dementia, including neuropsychiatric symptoms. • Cholinesterase inhibitors and memantine may be used for the treatment of cognitive impairment in vascular dementia, though effect sizes are small and may not be clinically significant. • No distinction made between cholinesterase inhibitors in efficacy.

Conclusions

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease (AD). Currently there are limited head-to-head trials comparing the efficacy of the cholinesterase inhibitors and no data comparing memantine to other agents used to treat AD. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has Food and Drug Administration approval for moderate-to-severe dementia of AD. It has also been studied as add-on therapy with donepezil and galantamine with results suggesting better tolerability than monotherapy. Although the addition of memantine to any current cholinesterase regimen may confer additional benefit, particularly in the area of tolerability and caregiver burden, the overall clinical impact of these agents are marginal.[23]

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Namenda® (memantine) is preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

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